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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,840	02/15/2002	Andrew J. Murphy	REG 780D	2776

7590 07/29/2005

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/076,840	Applicant(s) MURPHY ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *51-56,58,63-70 and 75*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

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Continuation of 11. does NOT place the application in condition for allowance because:
1. The Terminal Disclaimers over U.S. 6,586,251 B2 and 6,586,251 B2 are proper and have been entered.
2. The prior rejection of the claims under 112, 1st paragraph, for enablement, is withdrawn, in view of Applicants' Amendment to the claims, now reciting mouse ES cells.
3. The prior rejection of claims 51-55, 57-58, 63, 65-69, and 75 as being anticipated by Kuncherlapati et al. is maintained for reasons of record advanced in the prior Office action. Applicants argue that Kuncherlapati describe the introduction of standard targeting vectors by homologous recombination, or by random integration, of YACS into ES cells and that they do not disclose or suggest 1) homologous recombination of large DNA vectors equivalent to a LTVEC (for example, having homology arms greater than 20 kb) 2) targeted integration, 3) modifying an endogenous gene locus with site specific recombination sites, 4) site specific recombination sites lox P, lox511 and lox2272, or the use of a quantitative assay to detect a modified cell. Applicants submit that the Examiner has failed to establish that Kuncherlapati anticipate the claimed invention, because they teach using YACS, which are introduced by random integration, and that they fail to teach the use of quantitative assays, including quantitative PCR, to detect whether or not homologous recombination has occurred. Applicants argue that the DNA analysis by Southern blot or junctional PCR are not quantitative assays required by the claims, because they detect correct targeting by "qualitatively" probing across the homology arms of the targeting vector. Finally, Applicants argue that there is no teaching by Kuncherlapati with regard to the creation of flanking site-specific recombination sites. See pp. 8-9 of the Response. This is not persuasive. There is no requirement in the claims that require that the targeting vector have homology arms greater than 20 kb. Applicants argue arguing limitations that are not in the claims. See also, the prior Office action, p. 10, which specifically cites the instantly filed specification as support. Kuncherlapati teach using YACS, but they also teach that homologous recombination may be employed wherein the DNA is introduced into a particular loci (see pp. 14-15, bridging paragraph) which would be considered the targeted integration of a vector (see also, p. 10-11 of the prior Office action). With regard to Applicants' arguments that Kuncherlapati's teaching of Southern blotting is not considered quantitative, the specification itself supports utilizing Southern blotting as a technique for quantitative hybridization (see p. 30, lines 32-34).
4. The prior rejection of claims 51-56, 58, 63-70 and 75 as being obvious in light of Kuncherlapati when taken with Yang is maintained for reasons of record. Applicants' arguments, with regard to Kuncherlapati, are addressed above. Applicants argue that Yang do not teach the specific limitations of the claims; namely that neither of the reference describe the use of quantitative assays, including quantitative PCR, to detect whether or not homologous recombination has occurred. Furthermore, Applicants argue that the intention of Yang was not to homologously recombine their BAC-derived vectors, thus, there was no need to assay for homologous recombination, either qualitatively or quantitatively. Applicants argue that the quantitative MOA assay of the instant invention allows the identification of a modification made with any size DNA fragment, and that one could determine whether or not an allele of interest has been modified as desired within a period of a few hours. Applicants argue that there is no basis for stating that one of skill in the art could have a resonable expectation of success at arriving at the claimed invention. See pp. 10-11 of the Response. This is not found to be persuasive, as noted above, Kuncherlapati teach a quantitative assay, Southern blotting, which is supported by the specification as an assay that could be used for MOA screening. As stated in the prior Office action, Kuncherlapati differ from the claimed invention because they do not teach using bacterial homologous recombination, however, Yang teach using BACs to generate transgenic mice, and particularly for use in targeted recombination. Thus, it is maintained that the combination of Kuncherlapati and Yang provide the requisite teachings and motivation to arrive at the claimed invention.
5. The prior rejection of claims 51-55, 58, 63-69 and 75 is maintained as being obvious in light of Kuncherlapati when taken with Lie. Applicants' arguments, with regard to Kuncherlapati have been addressed above. Applicants argue that Kuncherlapati had no need to use a quantitative assay, such as Taqman, described by Lie, because when using targeting vectors, the homology arms were small enough for standard qualitative PCR, or Southern blot analysis, thus, there is no teaching or suggestion in the prior art to arrive at the claimed invention. See p. 11 of the Response. This is not persuasive. The teachings of Kuncherlapati and Lie are found to provide sufficient motivation and guidance to arrive at the claimed invention, as the Taqman technique, taught by Lie et al. can be used to quantify the number copies of a DNA template in a genomic DNA sample. Accordingly, the prior rejection of record is maintained.